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АПАТИНИБ СУПРЕССИРУЕТ ОПОСРЕДОВАННОЕ МАКРОФАГАМИ ПОВЕДЕНИЕ КЛЕТОК ГЕПАТОКЛЕТОЧНОЙ КАРЦИНОМЫ, МОДУЛИРУЯ ПЕРЕДАЧУ СИГНАЛОВ VEGFR2/STAT3/PD-L1[1]

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Гепатоклеточная карцинома (HCC) – наиболее часто диагностируемый первичный рак печени. В прогрессии опухолей могут участвовать опухолеассоциированные макрофаги, фенотипически сходные с макрофагами M2, которые секретируют цитокины, супрессирующие иммунный ответ опухоль-инфильтрирующих лимфоцитов. Изучена роль макрофагов M2 в прогрессии HCC и влияние ингибитора рецептора 2 фактора роста сосудистого эндотелия – апатиниба. В качестве модели HCC использовали клеточную линию Hepb3. Макрофаги M2 получены путем дифференцировки клеток THP-1. Для кокультивирования макрофагов M2 и клеток Hepb3 использовали ячейку Transwell. Жизнеспособность и пролиферативную способность клеток определяли методами CCK-8 и EdU. Метастатический потенциал клеток оценивали, используя метод определения миграции Transwell. Уровни экспрессии цитокинов определяли с помощью иммуноферментного анализа. Активацию оси VEGFR2/STAT3/PD-L1 количественно оценивали с помощью вестерн-блотинга. Показано, что сокультивирование с макрофагами M2 способствовало пролиферации, повышению жизнеспособности, продукции цитокинов, инвазии и миграции клеток Hepb3. При кокультивировании значительно увеличивалась секреция TGF-β1, IL-6, MMP-9 и VEGF. Апатиниб супрессировал индуцируемую макрофагами M2 пролиферацию, жизнеспособность клеток Hepb3, их инвазию и миграцию. Более того, апатиниб заметно снижал уровни экспрессии p-VEGFR2, p-STAT3 и PD-L1 в клетках Hepb3 в условиях кокультивирования. Таким образом, апатиниб может супрессировать опосредуемое опухолеассоциированными макрофагами поведение клеток HCC посредством модуляции сигнального пути VEGFR2/STAT3/PD-L1.

Ключевые слова: гепатоклеточная карцинома, опухолеассоциированные макрофаги, опухолевые клетки, апатиниб, VEGFR2

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Apatinib Suppressed Macrophage-Mediated Malignant Behavior of Hepatocellular Carcinoma Cells via Modulation of VEGFR2/STAT3/PD-L1 Signaling

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Hepatocellular carcinoma (HCC) is the most frequently diagnosed primary liver tumor worldwide. Tumor-associated macrophages (TAMs) usually have a similar phenotype to M2-like macrophages and can participate in tumor progression by secreting cytokines to suppress the immune response of tumor-infiltrating lymphocytes. We investigated the role of M2 macrophages in HCC progression and explored the effects of vascular endothelial growth factor receptor 2 inhibitor – apatinib . As a cellular model of HCC, Hepb3 cell line was used. M2 macrophages were obtained by differentiation of THP-1 cells. The Transwell chamber was used to co-culture M2 macrophages and Hepb3 cells. CCK-8 assay and EdU assay were conducted to measure cell viability and proliferation capacity. Transwell migration assay was conducted to estimate cellular metastatic potential. Cytokine expression levels were assessed by ELISA. Western blot was used to quantify the activation of the VEGFR2/STAT3/PD-L1 axis. It has been shown that co-culture with M2 macrophages increased, proliferation, viability, cytokine production, invasion, and migration of Hepb3 cells. The secretion of TGF-β1, IL-6, MMP-9, and VEGF was significantly increased after co-culture. Apatinib suppressed M2 macrophage-induced proliferation, cell viability, invasion, and migration of Hepb3 cells. Moreover, apatinib remarkedly decreased expression levels of p-VEGFR2, p-STAT3, and PD-L1 in Hepb3 cells under the co-culture conditions. In conclusion, apatinib treatment could suppress TAMs-mediated cancer cell behaviors of HCC cells via modulation of the VEGFR2/STAT3/PD-L1 signaling pathway.

Keywords: hepatocellular carcinoma, tumor-associated macrophages, cancer cell behaviors, apatinib, VEGFR2